Response

Claims 1-18-31, and 47 are pending.

Claims 32-46 have been canceled to expedite prosecution and without prejudice to their further prosecution in a separate application.

Claim 19 has been amended to incorporate the elements of original Claim 22 (now canceled).

Claim 47 has been added, as supported in the claims that have been considered by Examiner.

No new matter has been added with the amendments or the addition of the new claim. The scope of the claims is intended to be the same after the amendment as it was before the amendment.

Oath/Declaration

Applicant hereby resubmits a Declaration to overcome the Cavillo and Stamler references, which has been signed by both of the named inventors.

Rejection of Claims under 35 USC §§ 102(a) (Calvillo)

The Examiner rejected Claims 1-2, 4, 6-16, 18, 24, 29-30, 32-33, 38-40, and 43-46 under Section 102(a) as anticipated by Calvillo et al. (PNAS 100(8): 4802-4806, published on-line March 27, 2003, 10.1073/pnas.0630444100).

Without addressing or making any admissions regarding Calvillo, Applicant hereby re-submits a Declaration under Section 131(b) swearing behind Calvillo et al. Applicant conceived and reduced to practice the presently claimed invention prior to the Calvillo publication date of March 27, 2003.

Accordingly, withdrawal of this rejection of the claims is respectfully requested.

Rejection of Claims under 35 USC §§ 102(e) (Stamler)

The Examiner rejected Claims 1-8, 10-18, 24-31, and 46, and Claims 32-45 under Section 102(e) as anticipated by Stamler (US Publication 2004/0009908).

Without addressing or making any admissions regarding Stamler, Applicant hereby re-submits the enclosed Declaration under Section 131(b) swearing behind Stamler. Applicant

conceived and reduced to practice the presently claimed invention prior to the Stamler filing date of July 10, 2002.

Accordingly, withdrawal of this rejection of the claims is respectfully requested.

Rejection of Claims under 35 USC §§ 102(b) (Cynshi)

The Examiner rejected Claims 32-45 under Section 102(b) as anticipated by Cynshi (USP 4,732,889).

Without addressing or making any further admissions regarding Cynshi, Claims 32-45 have been canceled without prejudice to expedite prosecution of the method claims. Applicant reserves the right to pursue these claims in a separate application.

Accordingly, withdrawal of this rejection of the claims is respectfully requested.

Rejection of Claims under 35 USC § 103(a) (Stamler with Brines)

The Examiner rejected Claims 19-23 as obvious over Stamler in view of Brines (US Publication 2003/0134798). This rejection is respectfully traversed.

Applicant hereby re-submits the enclosed Declaration under Section 131(b) swearing behind Stamler. Applicant conceived and reduced to practice the presently claimed invention prior to the Stamler filing date of July 10, 2002.

Accordingly, it is submitted that, with the elimination of the prior reference (Stamler), this rejection cannot be maintained, and withdrawal of this rejection is requested.

As for Brines, the Examiner's statements regarding Brines at [0069] are *incorrect.*

In the Office Action at pages 3-4 the Examiner responded to Applicant's Response, stating as follows (emphasis added):

> The examiner acknowledges that Brines does not teach that the extension for transplant for an organ given can exceed the normal 30 hour time period by administering EPO to organs. However, this is just one aspect of what Brines teaches, specifically in the first line of paragraph [0069] it is stated:
>
> > "In another aspect of the invention a perfusate or perfusion solution is provided for perfusion and storage of organs for transplant, the perfusion solution including an amount of an erythropoietin effective to protect erythropoietin-responsive cells and associated cells, tissues *or organs*.

> Thus, the arugments [sic] from the previous office action in combination with Stamler et al. the rejection of the previous office action is maintained, because, administration of the EPO prior to transplantation can occur anywhere from 0-30 hours and beyond according to Brines, which still encompasses 5-30 minutes.

Nowhere does Brines teach *perfusing or administering* EPO to an organ for "0-30 hours."

In [0069], Brines merely states that a donor organ can be ***preserved*** for more than 30-hours (emphasis added):

> ...Using the solution, preservation may be extended beyond the 30-hour limit...

Brines does not state that EPO is *administered* for 0-30 hours.

The Examiner's interpretation of Brines' statement is in error.

The Examiner has failed to make a *prima facie* case of obviousness based on the cited references. Accordingly, withdrawal of this rejection is requested.

Information Disclosure Statement. Applicant brings to the Examiner's attention the enclosed Form 1449/PTO.

Applicant respectfully requests that these references be made of record in the present application, and that an initialed copy of the Form 1449/PTO indicating consideration of these references by the Examiner be returned to Applicant in the next communication.

Claim Fees. Please charge the required fees for any excess claims to Account No. 23-2053.

Extension of Term. The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply. Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that Applicant has inadvertently overlooked the need for a petition for extension of time. If any extension and/or fee are required, please charge Account No. 23-2053.

It is submitted that the present claims are in condition for allowance, and notification to that effect is respectfully requested.

Respectfully submitted,

Kristine M Strodthoff

Dated: August 5, 2005

Kristine M. Strodthoff, Reg. No. 34,259

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Appendix

Declaration under 37 CFR 1.131

Form 1449/PTO (1 sheet)

Copy of four (4) references

EXHIBIT A

ERYTHROPOIETIN, NITRIC OXIDE SYNTHASE AND RESISTANCE TO MYOCARDIAL ISCHEMIA

Rabbits adapted to chronic hypoxia exhibit increased resistance to myocardial ischemia, resulting from increased nitric oxide production from endothelial nitric oxide synthase (1). However, the sensor responsible for detecting hypoxia resulting in increased nitric oxide production is unknown. The adequacy of renal tissue oxygenation at Epo-producing sites regulates Epo production (2), but a more potent extrarenal oxygen sensor may exist (3). L-NAME partially blocks increase in plasma levels of Epo in mice following exposure to hypoxia, thus implicating nitric oxide in oxygen sensing and Epo production (4). Epo directly stimulates atrial natriuretic peptide secretion from adult rat atria but not cultured myocyte (5). These data suggest Epo may play a role in adaptation of hearts to chronic hypoxia and resistance to ischemia by a NOS related mechanism.

Hypothesis 1: Chronic hypoxia results in increased Epo production that subsequently controls nitric oxide production from NOS.

1. Measure Epo receptors in normoxic and hypoxic hearts.
   Availability of antibody to Epo

Hypothesis 2: Epo increases nitric oxide production from NOS3.

2. Treat normoxic rabbits acutely with Epo, is there an increase in nitric oxide production resulting in cardioprotection.

References

1. Shi Y, Pritchard Jr., KA, Holman P, Rafiee P, Griffith OW, Kalyanaraman B, Baker JE. Chronic myocardial hypoxia increases nitric oxide synthase and decreases caveolin-3. Free Radic Biol Med 29:695-703, 2000.

2. Kurtz A, Eckardt KU. Renal function and oxygen sensing. In: *Erythropoietin: Molecular, Cellular, and Clinical Biology*, edited by A.J. Erslev, J.W. Adamson, J.W. Eschbach, and C.G. Winearl. Baltimore, MD: Johns Hopkins University Press, 1991, P. 79-98.

3. Pagel H, Jelkmann W, Weiss C. O_2 supply to the kidneys and the production of erythropoietin. Respir Physiol 77:111-118, 1989.

4. Ohigashi T, Brookins J, Fisher JW. Interaction of nitric oxide and cyclic guanosine 3',5'-monophosphate in erythropoietin production. J Clin Invest 92:1587-1591, 1993.

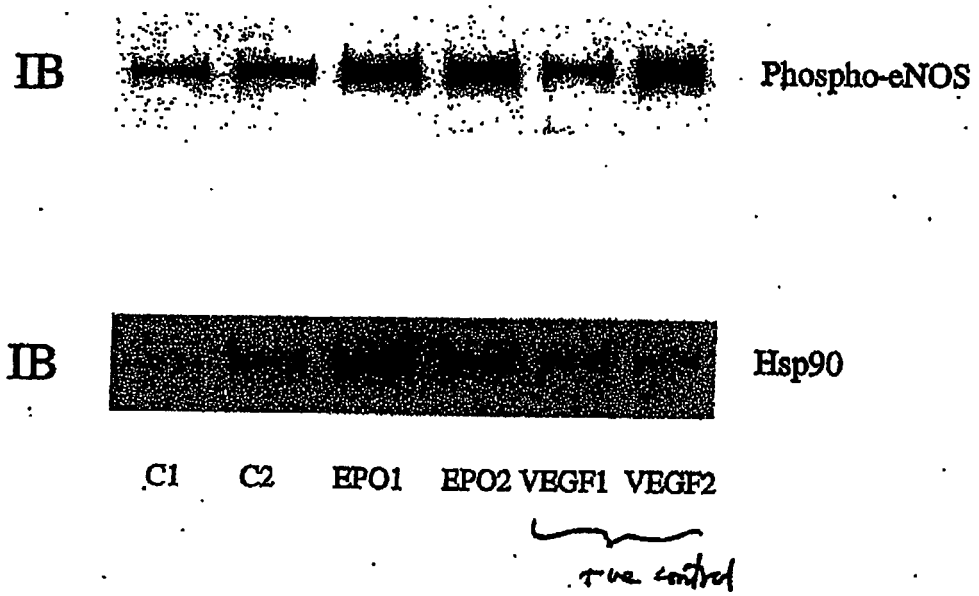
5. Porat O, Neumann D, Zamir O, Nachshon S, Feigin E, Cohen J, Zamir N. Erythropoietin stimulates atrial natriuretic peptide secretion from adult rat cardiac atrium. J Pharmacol Exp Ther 276:1162-1168, 1996.

John E. Baker, Ph.D.
[redacted] 2001

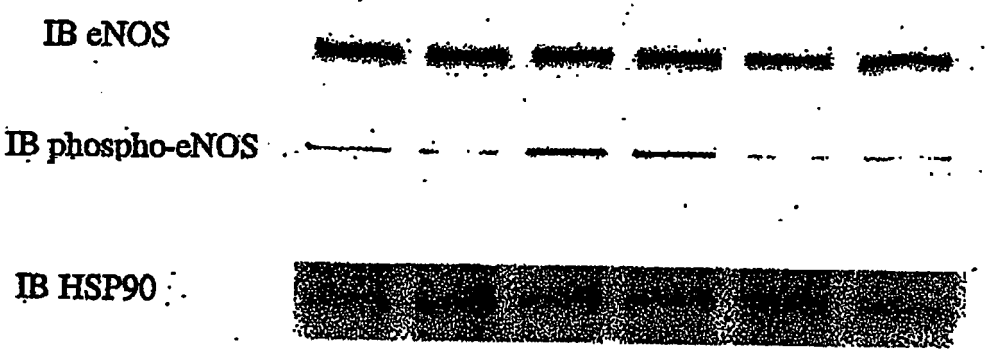
BCAE

EPO 5units/ml treatment for 24 hrs

IP eNOS



IP eNOS



		C1	C2	EPO1	EPO2	VEGF1	VEGF2
Ratio:	phospho-eNOS/eNOS	1		6.1		0.6	

Date: May 9, 2002

Exhibit B

MCW Research Foundation
Discovery Record and Report

1. Brief descriptive title: Cardioprotection by Erythropoietin

2. Full name of discoverer(s), home address(es), and position(s):

   a. John E. Baker, Ph.D., 2131 N. 72 St., Wauwatosa, WI 53213 Professor

   b. Yang Shi, Ph.D., 2116 N. 115 St., Wauwatosa, WI 53226 Post doctoral fellow

   c.

3. Results to be achieved by the practice of this discovery:

   Improved resistance of the heart to ischemia.

4. Brief description of the discovery: (Attach additional pages of description if necessary).

   See attachment

5. Chronology of conception and reduction to practice:

   a. Date of earliest conception: [redacted]

   b. Date of disclosure (orally or in writing) to other persons and names of such persons: [redacted]

   c. First written record pertinent to discovery: [redacted]

   d. Date and result of first test of the discovery: 12/19/01

6. Source, number and size of grant(s) used to support the research relating to this discovery:

   Departmental funding and NIH HL54075 $[redacted]

7. Date and place of publication or anticipated publication: (Attach copy of publication if available.)

   Autumn 2002

8. List any published information on known practices in the field of the discovery which is pertinent:

Witness: Mary Lynne Koenig

Discoverer: J.E. Baker

Name: John E. Baker, Ph.D. Date May 9, 2002

Yang Shi

Name: Yang Shi, Ph.D. Date May 9, 2002

Name: _____ Date

4. Brief description of the discovery

Erythropoietin is a key blood glycoprotein that initiates and regulates red blood cell production. Erythropoietin is approved by the FDA for human use in the treatment of anemia. We determined if erythropoietin can increase the resistance of the heart to ischemia. Hearts from New Zealand White rabbits were perfused with erythropoietin (0.5 – 10.0 U/ml) for 15 min prior to a global ischemic insult of 30 min followed by 35 min reperfusion. Erythropoietin exhibited a dose-dependent cardioprotective effect with optimal cardioprotection observed at 1.0 U erythropoietin/ml. Cardioprotection was manifest by a highly significant increase in recovery of pre-ischemic left ventricular developed pressure from 48±3% to 75±4%. We believe this is the first demonstration of cardioprotection by erythropoietin.